REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

In the Office Action dated February 20, 2002, the Examiner required restriction between claims drawn to variant HGF polypeptides (Group I, claims 31-41 and 49-54), claims drawn to variant HGF polypeptide antagonists (Group II, claims 42-44 and 55-57), claims drawn to methods of treating patients with HGF polypeptides and pharmaceutical compositions (Group III, claims 45-48) and claims drawn to polynucleotides encoding variant HGF polypeptides, vectors, host cells and methods of production (Group IV, claims 58-63).

Relying on EPO 757994, the Examiner took the position that Group I does not define a contribution over the art and "because the technical feature of the Group II-IV inventions are not present in the Group I claims, unity of invention is lacking". This basis for requiring restriction is not applicable to the instant claims.

First, claims 64-79 are novel and unobvious over EPO 757994. The Examiner clearly appreciates that such is the case as the Action does not include a rejection over EPO 757994. Further, and as regards claims 80-86, these claims recite the use of the same HGF polypeptides as claimed in claim 64. Given the commonality of technical feature, no basis for requiring restriction between claims 64-79 and claims 80-86 is seen. The Examiner is thus urged to reconsider his position and rejoin the claims.

Should the Examiner maintain his position for the present, he is nonetheless urged to rejoin method claims 80-86 at such time as claim 64-79 are found to be allowable.

Submitted herewith is a new oath/declaration. Entry of same is requested.

The claims (including claims 80-86) have been revised to define the invention with additional clarity. The claims as now presented make specific reference to the hairpin loop structure of human HGF as set forth in SEQ ID NO:3. The reference in the claims to SEQ ID NO:3 rather than SEQ ID NO:2 necessitated the numbering change.

Claims 64-79 stand rejected under 35 USC 112, first paragraph, as allegedly lacking written description. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The claims as now presented provide a structural definition of the hairpin loop of wild type human HGF. In addition, the meaning of human HGF would have been clear to one in the art at the relevant date. Thus, the situation with respect to the instant claims is distinguishable from Example 13 of the Revised Interim Utility Guidelines, to which the Examiner refers.

Example 13 of the Guidelines relates to a fact pattern wherein a variant of a specifically disclosed protein is claimed (i.e, claim 2 of the Example). The commentary of the Example states that the specification of the hypothetical fails to indicate what distinguishing attributes are shared by the members of the claimed genus. Moreover, the specification and claims of the Example are said to not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions to be made to the base

sequence (i.e., SEQ ID NO:3 of the Example 13). The commentary of the Example therefore concludes that the scope of the claim 2 includes numerous structural variants and that the claimed genus is "highly variant" because a significant number of structural differences between genus members is permitted." The commentary further indicates that the specification of the Example fails to provide guidance as to what changes in the structure should be made or describe structural features that could distinguish compounds in the claimed genus from others in the protein class. The commentary of the Example concludes that the claimed subject matter of the variant protein is not supported by an adequate written description because a representative number of species have not been described.

In the present invention, a positively charged amino acid in the hairpin loop structure of wild-type human HGF is replaced with a negatively charged amino acid. The entire amino acid structure of a wild-type human HGF was known prior to the filing date of the present application (see, for example, SEQ ID NO:2 set forth in the subject disclosure).

Unlike the facts of the hypothetical Example 13, the present specification describes a common structure for the claimed polypeptides containing a hairpin loop structure of a wild-type human HGF (i.e., as defined by amino acids 70-96 of wild-type HGF (page 6, lines 11-12 of the specification)) wherein a positively charged amino acid has been replaced by a negatively charged amino acid. The specification further defines positively charged amino acids as R (Arg), K (Lys), H (His) and negatively charged

amino acids as E (Glu) and D (Asp). See, page 6, lines 15-25 of the specification. The hairpin loop of the human HGR of SEQ ID NO:2 therefore is CANRCTRNKGLPFTCKAFVFDKARKQC or SEQ ID NO:3 which, as noted above, is recited in the claims as now presented. The positively charged amino acids of SEQ ID NO:3, for example, are amino acid residues 73, 76, 78, 85, 91, 93 and 94. See, page 7, last line through page 8, line 1 of the specification.

Thus , contrary to the Examiner's hypothetical Example 13, the presently claimed invention is supported by an adequate written description which describes a representative number of species. Moreover, while not believed to be necessary, the present specification describes polypeptides wherein Arg 73 has been replaced with Glu (R73E) or Asp (R73D), Arg 76 has been replaced with Glu (R76E) or Asp (R76D), and Arg 73 and Arg 76 have been replaced, for example, by Glu (R73E, R76E). Further polypeptides are described in the specification spanning page 7, last line through page 12. Example 1 of the specification describes a human HGF with amino acid replacements R73E, R76E and K78E. The specification defines a common core structure for HGF as well as a well defined genus of polypeptides.

As for the Examiner's reference to Fiers v. Revel (25 USPQ 2d 1601 (Fed. Cir. 1993)), the facts of present case are sufficiently distinct from those of Fiers so as to make the holding of the case inapplicable to the present application. Specifically, Fiers v. Revel relates to the conception and enablement of claims to a DNA molecule claimed *per*

se. The issue of conception of a DNA molecule was discussed relative to satisfaction of the written description requirement of § 112.

The case involved a three-way interference declared among three foreign parties – Fiers, Sugano, and Revel. The patents included claims to DNA that codes for human fibroblast beta-interferon (β-IF). The count of the interference was: "A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide."

Fiers' earliest patent application disclosed a method for isolating DNA coding β-IF, and, with a later filed application, disclosed the complete DNA nucleotide sequence coding for β-IF. Sugano's earliest patent application disclosed the complete DNA nucleotide sequence coding for β-IF and a method for isolating that DNA. Revel's earliest patent application disclosed a method for isolating a fragment of DNA for β-IF and a method for isolating the messenger RNA (mRNA) coding for β-IF, but did not disclose the DNA sequence coding for β-IF.

To determine which party was the first to conceive of the invention of the count, the court declared that conception of a substance claimed *per se* without reference to a process requires conception of the structure, name, formula, or definitive chemical or physical properties of the substance. In the case of a claim to a DNA molecule, the court stated that conception does not occur solely with definition of a method of preparation. The court further stated:

> The difficulty that would arise if we were to hold that a conception occurs when one has only the idea of a compound

> defining it by its hoped-for function is that would-be inventors would file patent applications before they had made their inventions and before they could describe them. That is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions, not of research plans. While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe the invention with particularity.

Sugano was found to have been the first to conceive the invention because the disclosure of the nucleotide sequence of the gene conveyed with reasonable clarity to those skilled in the art that as of the filing date. Sugano was in possession of the DNA coding for β-IF. Sugano's disclosure of the complete and correct nucleotide sequence of the DNA molecule coding for β-IF was also found to satisfy the written description requirement of § 112.

The court held that failure to disclose the actual DNA sequence, or other sufficient "definition" of the DNA molecule, constituted a failure to demonstrate conception. The court further held that failure to establish conception also constituted failure to establish enablement, stating that logically, one cannot enable an invention that has not been conceived.

The rule from Fiers is that conception of a DNA molecule claimed *per se* is not established until an adequate written description, either in the form of a structure, name, formula or definitive chemical or physical properties sufficient to distinguish it from other molecules, is disclosed. Fiers also teaches that disclosure of the nucleotide sequence of a DNA molecule is sufficient to satisfy the written description requirement of § 112, and is one way that conception of a DNA molecule can be established.

As noted above, and contrary to Fiers, the present application describes a number of species within the claimed genus. Moreover, the present specification provides more than idea of a compound, defined by only its hoped-for function, as was apparently only

present in Fiers' insufficient application. The Examiner's reference to Fiers is therefore misplaced.

The Examiner's reliance on Fiddes v. Baird, 30 USPQ 2d 1481 (BAPI 1993), is also not believed to be appropriate . In Fiddes v. Baird, the Board of Patent Appeals and Interferences held that party Fiddes' claims to a human gene for basic fibroblast growth factor were separately patentable over party Baird's issued and pending claims specifying a sequence encoding "mammalian" basic fibroblast growth factor.

The present application and claims are directed to polypeptides, not DNA sequences. Moreover, the present specification describes (and the claims recite) a wild-type human HGF hairpin loop sequence and human HGF was known at the time this application was filed. The issue in Fiddes related to the alleged lack of written description of a claimed DNA sequence from a disclosure of a polypeptide sequence.

Specifically, Party Baird's issued patent was based on an application filed at the time the protein had been sequenced, and it disclosed the amino acid sequence of the protein, which had been isolated from bovine pituitary and a theoretical DNA sequence encoding it. The pending claims were from a continuation-in-part application, presumably disclosing the naturally-occurring coding sequence for bovine fibroblast growth factor. Between the filing of the first application and the continuation-in-part application, DNA sequences anticipating claims to the naturally-occurring human fibroblast growth factor were published. Party Baird's position was that the published

sequences could not be used as prior art because it was entitled to rely on the filing date of the first application.

The Board held that party Baird was not entitled to the filing date of the first application for its claims to the mammalian DNA sequence because it did not set out specific DNA sequences of naturally-occurring mammalian genes in the first application and therefore did not meet the "written description" requirement of the patent statute. The Board stated that even with respect to the bovine gene for which the amino acid sequence was known, party Baird was "not in possession of the naturally occurring gene" at the time of filing the first application. The Board specifically stated that as of the relevant date (1987), knowledge of the amino acid sequence of a protein would not establish possession of the gene encoding the protein.

In Fiddes, the Board held the term "mammalian" was overly broad because "[t]he patent teaches no amino acid or DNA sequences for any mammalian FGF other than bovine pituitary FGF."

The holding of Fiddes is not applicable in the present case, however, for the reasons noted above. Specifically, for example, Fiddes involved a question of whether a disclosed amino acid sequence adequately described a gene or nucleic acid sequence encoding the same. The present application claims polypeptides wherein a defined hairpin loop structure is mutated in a specific and limited manner.

Similarly, the facts of University of California V.. Eli Lilly and Co., 43 USPQ 2d 1398 (Fed Cir. 1997) are not believed to be applicable to the present case, as the present

applicants are not claiming all mammalian DNA sequences which possess a specific function based on a disclosure of a single species, i.e., a rat sequence. Rather, Applicants have described a number of species within a well-defined genus, which is claimed by structure as well as function.

In view of the above, the Examiner is urged to reconsider his position. It is believed that having done so, he will find withdrawal of the rejection to be in order and same is requested.

Claims 64-79 stand rejected under 35 USC 112, first paragraph, as allegedly being non-enabled. Withdrawal of the rejection is submitted to be in order for the reasons that follow.

The Examiner's attention is directed to the fact that the claims as now presented recite a specific wild type hairpin loop structure in which a relatively small number of replacements (i.e., 128 possible combinations) can be made. Further, and as pointed out above, wild type HGF was known at the time of filing (again, attention is directed, for example, to SEQ ID NO:2 presented in the application). Accordingly, no undue burden would be placed on one wishing to practice the claimed invention and the Examiner's reliance on Rudinger is not believed to be well founded.

As regards the negative limitation in claims 74-77, the Examiner is reminded that an applicant can exclude from his claims subject matter so long as support for same is in the specification. Support for the instant negative limitation is found at page 18, line 11-

16. Accordingly, the claims do not attempt to claim the invention by excluding that which Applicants did not invent, as the Examiner suggests.

Reconsideration is requested.

Claims 64-79 stand rejected under 35 USC 112, second paragraph, as allegedly being indefinite. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions. Reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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